

Two decades into the crosstalk between bone and energy metabolism

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Aside from a few days around Halloween, the skeleton tends not to have a positive image. However, at least in the biomedical field, this view is changing as bone is now identified as an endocrine organ that positively regulates a broad range of key functions, including several aspects of energy metabolism.

In the beginning, there were no bones. Organisms were simple, importing nutrients by absorption. They then became increasingly complex, requiring specialized organs as well as regulations to control the needs and functions of those organs. Along with such evolution came the requirement for molecules to carry messages between organs, as well as the necessity to protect the organs from injuries. This is when the skeleton and exoskeleton emerged. For vertebrates, the skeleton became a protector of key organs, such as the brain, lungs, heart and marrow, as well as a facilitator for meeting these organs' energetic needs. Indeed, the skeleton allowed vertebrates to run, fly and climb to find food as much as to escape dangers. The success of the skeleton in achieving these tasks is best exemplified by the rapid proliferation and diversification of bony vertebrate species.

The trade-off, however, is that bone is expensive to build, maintain and repair. As anyone planning home remodelling knows, modifying a solid structure is costly because you cannot simply stretch or bend it; your only option is to destroy and rebuild it to the desired size or shape. The same applies for bones. To grow them or to adapt their shape means resorbing the existing mineralized matrix and depositing a new one. These functions are fulfilled by two bone-specific cell types: osteoclasts, which resorb mineralized matrix, and osteoblasts, which deposit new matrix. These complementary cell types are also recruited when bones fracture in a minute way during regular daily use or in a catastrophic, accidental way. To meet the heavy energetic cost of its constant remodelling, bone needs to signal to organs handling energy, such as the pancreas, liver, adipose tissue and, of course, the brain, which controls energy intake. So far, two bone-derived hormones that address this need have been identified: osteocalcin and lipocalin 2.

Osteocalcin (encoded by *OCN* and also known as bone γ -carboxyglutamate protein) was the first to be identified. It evolved with and is specifically synthesized by osteoblasts. Its functions, which are mediated by three known G-protein-coupled receptors (GPCR6A, GPR138 and GPR37), are as broad as its target organs. Osteocalcin regulates pancreatic β -cell proliferation and release of insulin, liver gluconeogenesis, insulin sensitivity and muscle function during exercise (Fig. 1). It also controls male fertility, the stress response and cognition but as this Comment focuses on metabolism, these functions will not be further discussed. Since the original identification of these functions using

Ocn-null mice, rodent models of cell-specific receptor inactivation, supplementation with exogenous osteocalcin studies and clinical correlations have largely confirmed these findings^{1–3}. More recently, studies in multiple mouse models demonstrated that maternal and embryonic osteocalcin synergize to optimize pancreatic β -cell proliferation, insulin secretion and liver gluconeogenesis in the offspring⁴.

Lipocalin 2 (encoded by *LCN2* and also known as neutrophil gelatinase-associated lipocalin) had been previously identified as a factor produced by adipocytes or in response to inflammation. Although it is not as bone specific as osteocalcin, osteoblasts produce as much as 70% of the lipocalin 2 in the blood circulation. A landmark study demonstrated via cell-specific gene inactivation that the bone-derived fraction of this hormone directly regulates glucose tolerance, insulin production, β -cell proliferation and appetite⁵ (Fig. 1). This study also identified melanocortin receptor 4 (MC4R) as lipocalin 2's target both in hypothalamic neurons and pancreatic β -cells. Here again, these findings were confirmed by subsequent animal studies and clinical correlative studies⁶.

All of the above could have prompted researchers in the field of evolutionary biology to search for molecules produced by bone cells that regulate energy metabolism. Yet, it was from the perspective of medicine that this notion emerged. At the turn of the twenty-first century, reasoning that obesity protects from osteoporosis whereas gonadal failure and starvation induce bone loss, Gerard Karsenty postulated that bone mass, energy metabolism, appetite and reproduction were mechanistically linked. Karsenty's hypothesis first led to the demonstration that the adipocyte hormone leptin acts on the brain's sympathetic tone to regulate bone remodelling⁷. The hypothesis subsequently led to the identification of osteocalcin not only as a regulator of glucose metabolism and lipolysis but also as a modulator of neuromediators, the parasympathetic nervous system and male fertility^{1,4,8}. In a sense, medicine drove biology to explore a new concept, and biology broadly extended its scope. With the demonstration that lipocalin 2 regulates appetite, all postulates of the original hypothesis are now supported by evidence.

The crosstalk between bone and energy metabolism has broad implications, most of them still incompletely defined. For instance, it would imply that failing bone health could be a threat to whole-body glucose homeostasis. Hence, pathologies or medications that weaken bones could have unintended metabolic repercussions. Supporting this notion, the glucose intolerance induced by glucocorticoid treatment, also a well-known cause of bone loss, is partly mediated by a decrease in levels of osteocalcin⁹. More studies are needed to define the scope of such 'off-target' effects. In a similar fashion, ageing and the negative consequences on bone health of sex steroid depletion could contribute to the changes in glucose handling that these physiological events also trigger.

Conversely, the body could recruit bone's ability to regulate glucose homeostasis to adapt to certain events. The best example yet of



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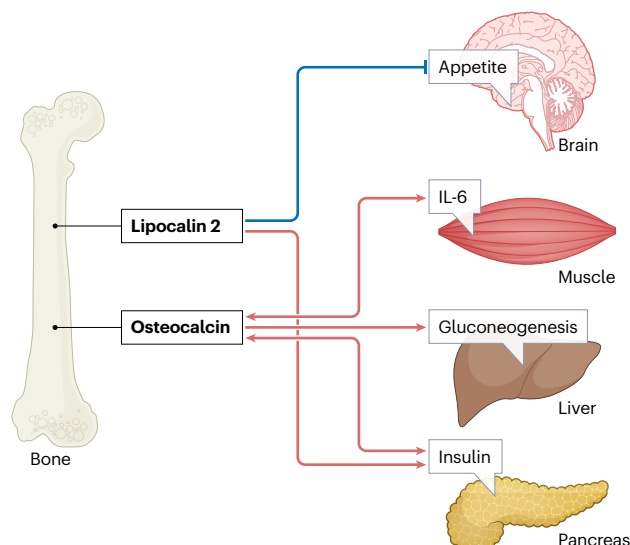


Fig. 1 | Schematic representation of the best understood endocrine regulators underlying the crosstalk between bone and energy metabolism. Bone engages in signalling with several key endocrine organs including the brain, muscle, liver and pancreas. Red arrows indicate activation; blue arrows indicate inhibition. IL-6, interleukin-6.

such recruitment occurs during exercise or intense life-saving activity (such as fleeing or fighting in response to danger or walking or climbing to gather food). In a feed-forward loop, interleukin-6 produced by myoblasts enhances the release of active osteocalcin from bone, which in turn promotes glucose uptake and utilization in myofibres and stimulates interleukin-6 production¹⁰ (Fig. 1). Both muscle and bone ‘synchronize’ for best performance. Other inter-organ cooperations could be defined by future studies.

The functional redundancies existing between osteocalcin and lipocalin 2 are also intriguing. They could exist simply because bone is so essential in fulfilling particular metabolic needs, during exercise, for instance. They could also reflect the ability of these hormones to be regulated by different signals associated with particular events that, in addition, might take advantage of the non-redundant functions between osteocalcin and lipocalin 2. Research into these signals and events as well as the recruitment of the bone endocrine machinery for therapeutic use should keep this emerging field busy for the next decade.

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Competing interests

The author declares no competing interests.